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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/744,176	06/18/2001	Christian Reiter	41317	3010

7590 11/06/2002

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EXAMINER	
LI, BAO Q	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 11/06/2002 9

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/744,176	REITER ET AL.	
	Examiner	Art Unit	
	Bao Qun Li	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *5-16 and 18-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1-21 are pending.

Sequence requirements

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. **In the instant case, the SEQ ID Nos of listed sequences in page 40 are missing.**

Full compliance with the sequence rules is required in response to this Office Action. A complete response to this office action should include both compliance with the sequence rules and a response to the Office Action set forth below. **Failure to fully comply with <u>both</u> these requirements in the time period set forth in this office action will be held non-responsive.**

Claim Objections

1. Claims 4 and 7 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot dependent from any other multiple dependent claim. See MPEP § 608.01(n). A proper correction of claim dependency is requested. Otherwise, the claims will not be further treated on the merits.

Election/Restrictions

1. Applicant's election with traverse of Group I, claim 1-14 and 17 in the scope of SEQ ID NO: 2 and 4 in Paper No. 8 is acknowledged. The traversal is on the ground(s) that Group I is direct to an antibody, whereas other groups V, X and VII are also direct to a pharmaceutical composition that can be deal with in a single search, without undue burden. This is not found persuasive because the compositions of Groups V and X are different from the product of Group I in that Group V comprises other components rather than an antibody, whereas the product of Group X comprise a polynucleotide other than the antibody of Group I. The search for Group I, does not need to search group V and X because the search for group I is deal with antibody and amino acid sequence, whereas the search for Group V deals with an antigen, the search for the

Group X deals with the nucleic acids. Moreover, the searching has to be conducted both in house and in commercial database and the source for searching is rather militated. Hence, it constitutes a serious burden.

2. Applicants further argue that the SEQ ID NO: 6 is only one amino acid different from SEQ ID NO: 2, should the election species, SEQ ID NO: 2 and 4, be found patentable, then examination of SEQ ID NO: 6 is required.

3. Applicants' argument has been respectfully considered; however, it is not found persuasive because different combinations of VL and VH can generate different antibodies, which exhibit different functions. Further, Applicants are reminded that the election of different sequences made in the previous office action is not a species election; there is no rejoin for the patentable different product with different structure.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-4 and 17 in the scope of SEQ ID NO: 2 and 4 is considered.

This application contains claims 5-16 and 18-21 drawn to an invention non-elected with traverse in Paper No. 8. A complete reply to the final rejection must include cancellation of non-elected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Applicants are also requested to amend the claims 1 and 3 to the scope of SEQ ID NO: 2 and 4 for reflecting the examination on the merits.

Claim Rejections - 35 USC § 101

Claim 1 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

In the instant case, claim 1, as written, do not sufficiently distinguish over antibodies as they exists naturally because claim 1 do not particularly point out any non-naturally occurring differences between the claimed antibody and binding composition and the structure of naturally occurring antibodies. It is well known that in during the HCV infection, antibodies against HCV E2 antigen are generated and the claims as currently recited encompass these naturally occurring compositions.

In the absence of the hand of man, the naturally occurring antibodies are considered non-statutory subject matter (Diamond v. Chakrabarty, 206 U.S.P.Q. 193 (1980)). It should be noted

that the mere purity of a naturally occurring product does not necessarily impart patentability (Ex parte Siddiqui, 156 U.S.P.Q. 426 (1966)). However, when purification results in a new utility, patentability is considered (Merck Co. v. Chase Chemical Co., 273 F.Supp 68 (1967), 155 USPQ 139, (District Court, New Jersey, 1967)). Amendment of the claims to recite "an isolated or purified" antibody or similar language would obviate this rejection.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-4 and 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claim 1 is unclear and confusing in that the claim fails to define precisely what at least one and other complementary determining regions (CDR) of the V_H and V_L are. Applicants are reminded that the method for making a monoclonal antibody or chimeric antibody or an antibody fragment by CDR grafting requires 3 pairs of defined CDRs and four defined framework regions (FRs) in combination with constant regions to create variety of an antibody that bind to the same antigen epitope, wherein the defined 3 CDRs and FRs form a loop-like structure for contacting with an antigen, holding it in place as taught by Bendig et al. (METHODS: A companion to Methods in Enzymology 1995, Vol. 8, pp. 83-93). If Applicants wish to claim an antibody or a series of this antibody derivatives made by a defined group of CDRs and FRs, the claim should point out what all precise sequences of the 3CDRs and 4FRs are or where are they located in the disclosed sequences. Otherwise, the claim is considered indefinite.

Claims 1 and 4 are vague and indefinite in that the metes and bounds of a conformation-dependent epitope of Hepatitis C virus glycoprotein E2 are not defined. The claim is interpreted in light of the specification; however, the specification does not teach what the definition of the conformational-dependent epitope is and what the sequence structure of the conformational-dependent epitope is. Because Hepatitis C virus (HCV) is an RNA virus, which is subjected to

mutated frequently and automatically. Therefore, the sequences of HCV is highly divergent and have many quasispecies from one isolate to another or from one type to another type, especially the HCV E2 comprise a hypervariable region at the N-terminus of the NS1/E2 junction as evidenced by Field (Fields Virology edited by Fields et. al. 1995, Vol. 1, lines 1-60 on right col., page 1039) and Okamato (Virology 1992, Vol. 188, pp. 331-341). Furthermore, HCV E2 protein ranges from about amino acid 384 to amino acid 746, there are many antigen epitopes comprised among these more than 300 amino acid residues. Therefore, claims should point out precisely which conformational-dependent E2 epitope is intended in the claims.

7. The claim 1 is also vague for recitation of a relative word "capable of", because the capability of a compound or composition to perform some function is merely a statement of a latent characteristic of said compound or composition and said language carries no patenable weight. Therefore, the claims are regarded as indefinite.

8. Claim 2 is confusing for further defying the antibody of claim 1 as a polyclonal antibody. Because the polyclonal antibody is raised against multiple antigen epitopes and is unable to be determined by complementary determining region.

9. Claim 17 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: how the assay is performed, such as when the antibody is added into the cells, how many antibody is used and how long the incubation is required etc.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-4 and 17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for having a human anti-HCV E2 antibody having a defined V_L of SEQ ID NO: 2 and a defined V_H of SEQ ID NO: 4, wherein the antibody is able to bind the HCV E2 antigen, precipitate the E1/E2 associated complex, and block the E2 binding to the

target cells, does not reasonably provide enablement for any or all kind of antibody or antibody fragment that is able to is able to bind the HCV E2 antigen, precipitate the E1/E2 associated complex, and block the E2 binding to the target cells . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The test of scope of the enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art would undue experimentation (See United States v. Theketronic Inc., 8USPQ2d 1217 (fed Cir. 1988). Whether undue experimentation is required is not based upon a single factor but rather a conclusion reached by weighting many factors. Theses factors were outlined in Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and gain in re Wands, 8USPQ2d 1400 (Fed. Cir. 1988).

1) & 2) State of art and unpredictability:

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences, which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc. Natl. Acad.Sci .USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function.

3) & 4) Number of working examples and amount of guidance.

As making a monoclonal antibody or fragment of an antibody requires three pairs of defined CDRs and four pairs of defined framework regions (FRs) as described supra (Rudikoff et al. and Bendig et al. Applicants do not teach what the 3 pairs of CDRs and four pairs of the framework regions (FRs) are or precisely where they are located.

Applicants also fail to teach how the conformational-epitope of the HCV E2 is determined and what the precise sequence structure is.

The specification does not have a disclosure of any or all antibodies or antibody fragment as listed in the claim 2 that comprises at least one CDR. Especially, a polyclonal antibody since polyclonal antibody does not have a single bind domain of an antigen.

5) Scope of the claims.

The scope of the claims broadly read on any or all antibodies or antibody fragment recognize the HCV E2, precipitate E1/E2 associated complex and inhibit the E2 binding to the target cells.

6) & 7) Nature of the invention and Level of the skill in the art.

The nature of the invention is directed a human antibody or series of antibodies made by defined 3 pairs of CDRs and 4 FRs in V_L and V_H regions, The level of the skill for using CDRs and FRs to make antibody or antibody fragment is very sophisticated and high. Without adequate teaching and guidance, it would have to require a skill in the art to do undue experimentation.

Given the above analysis of the factors, which the courts have determined are critical in asserting whether a claimed invention is enabled, it must be considered that the skilled artisan would have to conducted undue and excessive experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

13. Claims 2 and 4 are rejected under 35 U.S.C. 102(a) as being anticipated by Nakano et al. (J. Virol. 1997, Vol. 71, pp. 7101-7109).

14. Nakano et al. disclose a series of monoclonal antibodies generated by using HCV E2 envelope protein amino acid 384-746 residue or 5 fragments of this sequence fused with HBV pre-S2 respectively. It has been noted that these antibodies were able to bind to the same antigen as disclosed in the present application and precipitated with the HCV E1/E2 associated complex antigen as is disclosed or claimed in the present application. (See Fig 1 on page 7103, Fig 3 on page 7105, and Fig 5. on page 7107.). Therefore, the claimed invention is anticipated by the cited reference.

15. Claims 4 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Persson et al. (WO 97/40176).

16. Persson et al. explicitly teach methods for making the monoclonal antibody against HCV E2 antigen, wherein the antibody made by Persson et al. is able to recognize the same E2 antigen as disclosed in the present application and is able to precipitate E1/E2 antigen complex. Persson also teach an assay for using the isolated antibody or fragment of the antibody to block the HCV E2 binding to the target cells and subclone the HV- and VL region and sequence these critical regions. (See examples 6-8 from page 64-69, example 12 on page 74-75, and claims 1, 2, 6, 8, 9, 10). Therefore, the claimed invention is anticipated by the cited prior art.

17. Claim 4 is rejected under 35 U.S.C. 102(b) as being anticipated by Cardoso et al. (J. Medi. Virol. 1998, Vol. 55, pp. 28-34).

18. Cardoso et al. disclose several human monoclonal antibodies (HmAbs) generated by EBV transformation of PBMC from HCV infected blood donor, After this anti-HCV antibody producing lymphoblostoid cells (LCL) fused with the heteromyoloma cell line K6H6/B5, 15 antibody-producing heterohybridomas have been yield. Several HmAbs produced by this method are able to bind HCV E2 and E2/E1 antigen and inhibit the E2 binding in the competitive assay (see entire document). Therefore, the claimed invention is anticipated by the cited reference.

19. Claim 17 is rejected under 35 U.S.C. 102(b) as being anticipated by Burioni et al. (Hepatology 1998, Vol. 28, pp. 810-814).

20. Burioni et al. explicitly teach methods for making the human monoclonal recombinant Fab fragment specific for hepatitis C virus E3 envelope protein. The sequences for the HCV/E2

protein were cloned and characterized. Burioni also teach an assay for testing the cloned antibody fragments to inhibit the HCV E2 binding to the target cells (See entire document). Therefore, the claimed invention is anticipated by the cited prior art.

Claim Rejections - 35 USC § 102

21. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

22. Claim 4 is rejected under 35 U.S.C. 102(b) as being anticipated by Deleersnyder et al. (J. Virol. 1997, Vol. 71, pp. 697-704).

23. Deleersnyder et al. explicitly teach methods for making the monoclonal antibody against HCV E2 antigen, wherein the antibody made is able to recognize the same E2 antigen as disclosed in the present application and is able to precipitate E1/E2 antigen complex (See entire document). Therefore, the claimed invention is anticipated by the cited prior art.

24. Claim 4 is rejected under 35 U.S.C. 102(b) as being anticipated by Rosa et al. (P.N.A.S. USA, 1996, Vol. 93, pp. 1759-1765).

25. Rosa et al. explicitly teach methods for making the monoclonal antibody against HCV E2 antigen, wherein the antibody made by Rosa is able to recognize the same E2 antigen as disclosed in the present application and is able to precipitate E1/E2 antigen complex. Rosa et al. also teach the assay for using the isolated antibody or fragment of the antibody to as well as block the HCV E2 binding to the target cells (See entire document). Therefore, the claimed invention is anticipated by the cited prior art.

Claim Rejections - 35 USC § 103

26. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

27. Claims 1-4 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cardoso et al. (J. Medi. Virol. 1998, Vol. 55, pp. 28-34) and Persson et al. (WO 97/40176).

28. Claimed invention are drawn to a human monoclonal antibody (HmAb) of HCV E2, wherein the antibody against HCV E2 antigen 371-746 of prototype strain H (genotype 1a) is generated by EBV infected PBMC cells isolated from the HCV infected patients. This anti-HCV antibody producing lymphoblostoid cells (LCLs) were further cloned. The 2 human monoclonal antibodies were produced and tested for being able to precipitate the E2/E1 associated complex and inhibit the E2 binding to the target cells. The cloned heavy- and light chain fragments were subsequently sequenced as SEQ ID NO: 2 and 4.

29. Cardoso et al. disclose several human monoclonal antibodies (HmAbs) of HCV E2 generated by EBV transformation of PBMC from HCV infected blood donor, After this anti-HCV antibody producing lymphoblostoid cells (LCL) were fused with the heteromyoloma cell line K6H6/B5, 15 antibody-producing heterohybridomas have been yield. Several HmAbs produced by this method are able to bind HCV E2 and E2/E1 associated antigen complex and inhibit the E2 binding in the competitive assay (see entire document). Cardoso et al. does not explicitly teach to the assay of inhibiting the E2 binding to the target cells and sequencing the VH- and VL chains of the antibodies.

30. Persson et al. explicitly teach the assay for using the isolated antibody of HCV E2 or fragment of the antibody to block the HCV E2 binding to the target cells and the method for sub-cloning the Fab fragment comprising the VH- and LV regions and sequencing these regions. Perssson et al. also teach how to prepare the specific binding regions of Fab fragment clone comprising the critical VH- and VL sequence for testing its HCV E2 or HCV E2/E1 complex antigen reactivity and inhibiting HCV E2 binding to the target cells too (See entire document).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention was filled to be motivated by the recited references to isolate anti-HCV E2 antibody by using the method taught by Cardoso et al. to isolate a HmAb and further adapting the method of

Persson et al. to test the antibody reactivity with E1 and E2/E1 complex or inhibitory activity against E2 binding to the target cells or to sequence the VH- and VL region if the antibody exhibit a good inhibitory effect against HCV E2 binding to the target cells as taught by Persson without highly expected success. Hence the claimed invention as a whole is prima facie obvious absence unexpected results.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bao Qun Li whose telephone number is 703-305-1695. The examiner can normally be reached on 8:00 to 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Bao Qun Li
October 30, 2002

JAMES HOUSEL 11/3/02
SUPERVISORY PATENT EXAMINER
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